Complete Summary

GUIDELINE TITLE

Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support.

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Imrie K, Makarski J, Esmail R, Meyer R. Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Oct [online update]. 35 p. (Practice guideline report; no. 6-6). [106 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Multiple myeloma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use of high-dose chemotherapy and peripheral stem cell or bone marrow transplantation for patients with multiple myeloma

TARGET POPULATION

Adult patients with advanced-stage multiple myeloma and good performance status

INTERVENTIONS AND PRACTICES CONSIDERED

1. Conventional chemotherapy with oral melphalan and prednisone
2. Multi-agent intravenous chemotherapy including a combination of one or more alkylating agents, such as melphalan, BCNU (carmustine), or cyclophosphamide (e.g., VMCP/BVAP [vincristine, melphalan, cyclophosphamide, and prednisone/vincristine, carmustine, doxorubicin, and prednisone])
3. High-dose glucocorticoid-based chemotherapy, such as vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD), without alkylating agents
4. Interferon alpha

   Note: The guideline developers were unable to reach consensus about the use of interferon.

5. Total body irradiation (TBI)

   Note: For patients undergoing autologous stem cell transplantation as part of standard therapy, it is recommended that the transplantation regimen include melphalan without total body irradiation.

6. Allogeneic bone marrow transplantation (alloBMT)

   Note: Allogeneic transplantation is not recommended outside of a clinical trial.

7. Autologous bone marrow transplantation (ABMT)
8. Peripheral blood stem cell transplantation (PBST)
9. Early versus late transplantation
10. Single versus double (i.e., tandem) transplantation

    Note: Tandem transplantation is not recommended outside of a clinical trial.

MAJOR OUTCOMES CONSIDERED

- Response rates to treatment
- Survival (overall, median, event-free, or progression-free)
- Treatment-related toxicity and mortality
- Incremental effectiveness (ratio of incremental cost and incremental effectiveness)

- Marginal cost-effectiveness ratio
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original 2000 Guideline

MEDLINE, CANCERLIT and the Cochrane Library databases were searched from 1992 to December 1997. This search was updated in October 1998, June 1999, and April 2000. "Multiple myeloma" (MeSH and text word) was combined with "bone marrow transplantation" (MeSH and text word) and drug therapy (MeSH). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, controlled clinical trials and comparative studies. In addition, Pubmed, the Physician Data Query (PDQ) database, relevant conference proceedings (American Society of Hematology, 1997, 1998, 1999 and American Society of Clinical Oncology, 1999), article bibliographies, and personal files were reviewed. To address the issue of optimal chemotherapy, an additional search was performed of the same databases using "multiple myeloma" (MeSH) combined with "randomized controlled trials" (MeSH) and the text word "random:" in the title.

October 2003 Update

The original literature search has been updated using MEDLINE (Ovid) (through March 2003), Medline® In-Process & Other Non-Indexed Citations (formerly known as PreMedline) (PREM) (March 13, 2003), CANCERLIT (Ovid) (through October 2002), the Cochrane Library (2003, Issue 1), the proceedings of the annual meetings of the American Society of Clinical Oncology (2000 to 2002) and the American Society of Hematology (2001 and 2002), and the abstracts of the VIIIth International Myeloma Workshop. The PDQ (http://www.cancer.gov/search/clinical_trials/) (January 8 and 9, 2003), National Institutes of Health Clinical Trials.gov (http://clinicaltrials.gov/) (January 21, 2003), United Kingdom Coordinating Committee on Cancer Research Register (http://www.ctu.mrc.ac.uk/ukcccr/register_new.htm) (January 21, 2003), and European Organization for Research and Treatment of Cancer (http://www.eortc.be/) (January 21, 2003) clinical trials databases were also searched to determine the status of the ongoing trials reported in the original practice guideline report and to search for any new ongoing trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) (January 8, 2003) and the National Guidelines Clearinghouse (http://www.guideline.gov) (January 8, 2003) were searched for existing evidence-based practice guidelines.

Personal files were also reviewed; in May 2003, the fully published results of the Medical Research Council (MRC) Myeloma VII trial became available, so we included the trial in the June 2003 update.

Inclusion Criteria

Articles were selected based on the following criteria:

1. Randomized controlled trials (RCTs) of patients with multiple myeloma that reported on the outcomes of survival and/or quality of life
2. Non-randomized trials were included if they had appropriate contemporaneous control groups and reported on the outcomes of survival and/or quality of life.

Study results were used to estimate both the potential efficacy and appropriate timing of autologous and allogeneic transplantation. Meta-analyses, systematic reviews, and economic analyses were also included. Because of insufficient data addressing the specifics of the transplant manoeuvre and which patients would be most likely to benefit from transplantation, a second literature search was performed to include data from single-arm studies.

October 2003 Update

As of the June 2003 guideline update, only RCT data will be included except for the questions addressing the relative efficacy of autologous and allogeneic transplantation and pretransplant chemotherapy. In addition, updated data for nonrandomized trials already included in the guideline will be reported.

NUMBER OF SOURCE DOCUMENTS

Original 2000 Guideline

69 papers met the criteria for inclusion.

October 2003 Update

26 reports were identified in the update process.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

2000 Guideline

As the nine randomized controlled trials on transplantation addressed different questions, statistical pooling of data was not attempted.

2002 Update

The Disease Site Group (DSG) recognized that the pooling of data comparing standard-dose therapy with high dose therapy and autologous transplantation may be feasible. The Disease Site Group will review whether conducting a published data meta-analysis is appropriate when the results of recently reported abstract publications are reported in article form.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original 2000 Guideline

The Hematology Disease Site Group (DSG) was asked to develop a broad guideline on the management of patients with multiple myeloma. The DSG considered the potential of developing a more comprehensive guideline and concluded that the complexity and importance of the high-dose therapy transplant topic warranted a specific guideline; the possibility remains for subsequently merging this guideline into a document dealing with a wider range of issues in myeloma.

On appraising the published literature regarding transplant therapy, there were two major issues that yielded considerable debate. The first issue related to the quality and volume of data assessing the transplant question. Specifically, debate centered on the strength of the recommendation for transplantation given that the supporting data were limited to only one well-conducted positive randomized trial. After careful consideration, there was unanimous agreement that patients ought to be informed about the results of this study and this was reflected in the wording of the recommendations. There was further discussion about whether there was sufficient evidence to not only offer, but to "recommend" this treatment as the preferred therapeutic option. While the DSG felt that patients should have a choice, they felt that that the current evidence is sufficient to warrant the "recommend" terminology.

The second point of debate dealt with the role of interferon. Some members of the group felt that as interferon was part of the treatment maneuver in the Attal study, and was reported by Cunningham et al to result in superior time-to-disease

progression, the use of interferon should be included in transplant treatment strategies. Other members felt that in the absence of data demonstrating a survival advantage, the toxicity of this agent precludes routine use. The DSG was unable to reach consensus, and a recommendation about using interferon was therefore not included.

The DSG members considered whether a firm recommendation should be made regarding the timing of transplantation. Members felt that the best available evidence found a survival benefit when transplantation was used as part of the initial therapy. In a randomized trial of early versus delayed transplantation in patients in whom stem cells had been collected at diagnosis, delaying transplant did not shorten survival although there was a suggestion that quality of life was adversely affected; however the 95% confidence intervals overlapped. For this reason, the DSG members did not feel that a strong recommendation could be made regarding the timing of transplantation, although there was consensus that if a delayed transplant is contemplated, stem cells should be collected soon after diagnosis.

The initial draft recommendations were circulated for practitioner feedback in May 1999 and received wide support. The initial Practice Guideline was approved by the Practice Guidelines Coordinating Committee in October 1999. Since the release of the initial guideline, new data emerged in abstract form that included assessment of the role of total-body irradiation (TBI) and a further randomized trial evaluating autologous transplantation in patients over age 55 years.

The DSG concluded that the study comparing melphalan 140 mg/m^2 plus total-body irradiation with melphalan 200 mg/m^2 required modification of the previous recommendation regarding the details of the high-dose therapy regimen (bullet five). The reworded recommendation now permits either option (see "Major Recommendations" field). There was considerable discussion regarding the results of the report by Fermand et al. This trial, published in abstract form, compared a transplant strategy with standard dose treatment in patients 55 years and greater and failed to detect a survival benefit. The DSG considered whether these data should lead to a rewording of the overall recommendation regarding "offering" versus "recommending" high-dose therapy transplantation and/or whether an age restriction should be suggested. The DSG concluded that while the Fermand trial was large and appeared to be well conducted, insufficient information was provided in the abstract to change the initial recommendations. However, the wording of the new recommendation (bullet one) highlights the indication by age. The DSG acknowledges that the final results of the Fermand trial and other ongoing studies may influence the nature and wording of the recommendations in the future.

The DSG did not consider these new data and the resulting modifications sufficiently different from the initial guideline to warrant another cycle of practitioner feedback. This revised guideline was circulated to the Practice Guidelines Coordinating Committee.

October 2003 Update

The Hematology DSG's evaluation of new evidence resulted in extensive discussions of two topics: the role of autologous stem cell transplantation in

comparison with standard-dose therapy and the nature of the high-dose therapy regimen.

The publication of the Medical Research Council (MRC) trial has strengthened the evidence in favor of high-dose therapy and autologous transplantation over standard dose therapy for newly diagnosed patients with myeloma. While a meta-analysis will be required to better define the magnitude of benefit, the DSG concluded that high-dose therapy should continue to be recommended for patients with myeloma and that the text of the recommendation should be amended to indicate that the evidence is strongest in patients under the age of 65 years.

Given the updated evidence regarding high-dose therapy preparative regimens, the DSG unanimously concluded that melphalan 200 mg/m^2 as a single modality should be the recommended regimen for patients undergoing autologous transplantation outside a clinical trial setting. In comparison with melphalan 140 mg/m^2 and total body radiation, melphalan given as 200 mg/m^2 was associated with superior survival and less toxicity, and was less resource intensive.

The DSG discussed whether the publication of the Attal study should lead to a change in the recommendation regarding double (tandem) autologous transplantation. The DSG concluded that the survival benefit reported in that trial was potentially important, but noted that other trials did not report a benefit. The DSG also noted that the high-dose therapy regimen used in the single transplant arm in that trial no longer represents the standard of care, as it has been shown to be inferior to melphalan (200 mg/m^2) alone. The DSG members concluded that the recommendations should not be changed until new data are available from those studies. The DSG concluded that new evidence regarding the role of post-transplantation interferon maintenance did not warrant a change in the recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A cost-effectiveness analysis using survival data reported in five large published randomized controlled trials on induction treatment evaluated the incremental cost-effectiveness ratio [the ratio of incremental cost and incremental effectiveness (where incremental cost is the lifetime cost difference between treated patients and controls, and incremental effectiveness is the lifetime survival difference between the two patient groups)]. The mean lifetime duration of survival was 3.47 years for melphalan at conventional doses without interferon, 3.74 years for melphalan at conventional doses with interferon, and 7.28 years for autologous bone marrow transplantation (ABMT). Survival was significantly better for patients undergoing ABMT versus melphalan treatment (relative risk reduction = 54%, 95% confidence interval [CI], 46% to 59%; $p<0.05$). Survival after combined melphalan and interferon treatment was not significantly different from melphalan alone ($p>0.05$). The marginal cost-effectiveness ratio of autologous transplantation was approximately an additional $26,000 per life year gained compared with conventional treatment with melphalan.

Economic analyses based on trials that collect data on cost as part of their primary data collection are less susceptible to methodological errors. This economic analysis collected and pooled data from information available in the published literature. Based on the critical appraisal done by the Guidelines Initiative, the guideline developers have determined it to be methodologically rigorous. Therefore, the impact of ABMT compared with conventional treatment with melphalan can be considered to be favourable in terms of cost-effectiveness ratio.

One study involved a cost-minimization analysis to compare peripheral blood stem cells (PBSC) transplantation with ABMT and another included costing data in a non-randomized comparison that assessed tolerance in interferon post-transplant as its primary outcome parameter. Both analyses demonstrated that PBSC transplantation had economic advantages when compared with ABMT.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Original 2000 Guideline

Practitioner feedback was obtained through a mailed survey of 221 practitioners in Ontario (94 hematologists, 93 medical oncologists, and 24 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Hematology Disease Site Group.

The practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Hematology Disease Site Group and the Practice Guidelines Coordinating Committee.

October 2003 Update

The recommendations regarding autologous transplantation and high-dose regimens have been modified to reflect the updated evidence. The changes in recommendations were not sent for external review because they did not substantially deviate from the original recommendations.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Autologous transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients

under 65 years of age without significant renal dysfunction following hydration and remission-induction chemotherapy. Physicians must use their clinical judgment in recommending transplantation to patients over 65 years of age or those with renal impairment.
- There is insufficient evidence to recommend allogeneic transplantation as routine therapy for multiple myeloma. Patients who are potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not be given extensive exposure to alkylating agents such as melphalan prior to the collection of stem cells. High-dose glucocorticoid-based regimens such as vincristine, doxorubicin (Adriamycin), dexamethasone (VAD) are preferable for such patients.
- Harvesting of autologous peripheral blood stem cells or bone marrow should be performed early in the patient´s treatment course. The best available data demonstrate that transplantation is most advantageous when performed as part of the initial therapy.
- No conclusions can be reached about the role of interferon alpha following transplantation at this time.
- For patients undergoing autologous stem cell transplantation as part of standard therapy, it is recommended that the transplantation regimen include melphalan 200 mg/m^2 without total body radiation.
- There is insufficient evidence to recommend a treatment plan that includes two transplants performed in succession (tandem transplantation) outside of a clinical trial.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized controlled trial (RCT) found autologous bone marrow transplantation (ABMT) prolonged survival in newly diagnosed patients under the age of 65 with advanced stage disease compared with conventional chemotherapy with interferon alpha (five-year survival, 52% versus 12%; p = 0.03).
- In terms of the specifics of the manoeuvre, a randomized controlled trial in abstract form comparing bone marrow to peripheral bloods stem cell infusion found that neutrophil engraftment was faster for patients receiving peripheral blood stem cells (9.7 days versus 12.2 days; p<0.001); however, toxic death rates, response rates, and two-year survival were not significantly different; an RCT in abstract form that compared high-dose melphalan plus total body irradiation versus high-dose melphalan did not find a difference in terms of

response and two-year event-free survival, but toxicity was significantly greater for patients receiving the total body regimen; two RCTs in abstract form of single versus double bone marrow transplantation did not find a significant difference in progression-free survival or overall survival between the two groups. An RCT on interferon following transplantation found that there was a non-significant trend towards longer median progression-free survival in the patients given interferon (46 months vs. 27 months; p = 0.11); however, there was no difference in overall survival.

- One randomized controlled trial on early versus late transplantation found the median survival was 64.6 months for early transplant and 64 months for late transplantation (p = 0.92). The quality of life measure, TWISTT (time-without symptoms, treatment and treatment toxicity) was 27.8 months (95% confidence interval, 23.8 to 31.8) in the early transplant group versus 22.3 months (95% confidence interval, 16.0 to 28.6) in the late transplant group.
- Three non-randomized comparisons of autologous and allogeneic transplantation found autologous transplantation to be less toxic and associated with at least equivalent survival.

October 2003 Update

- In an updated report of the randomized trial comparing combination therapy with melphalan 140 mg/m^2 and total body irradiation (TBI) with melphalan 200 mg/mg^2 as a single modality, survival at 45 months was superior in the group assigned to receive melphalan 200 mg/mg^2 (65.8% versus 45.5%; p=0.05). In addition, patients assigned to receive melphalan 200 mg/mg^2 experienced less severe mucositis, required fewer transfusions, and had shorter durations of hospitalization and intravenous antibiotic administration.
- In addition to the single RCT comparing high-dose therapy and stem cell transplantation with conventional chemotherapy identified in the original document, three more RCTs have been published. Two of the four studies reported a survival benefit for patients randomized to receive high-dose therapy and autologous stem cell transplantation.

POTENTIAL HARMS

- Treatment-related mortality is a significant problem with allogeneic transplantation. Three non-randomized comparisons of autologous and allogeneic transplantation found autologous transplantation to be less toxic and associated with at least equivalent survival.
- The effect of prior alkylating agent exposure on bone marrow harvesting is not clear. However, alkylating agent exposure adversely affects peripheral blood stem cell yield and engraftment following autologous stem cell transplantation (ASCT). If stem cell transplantation is considered, patients should not be given extensive exposure to melphalan or other alkylating agents prior to stem cell collection. High-dose glucocorticoid-based regimens such as VAD (vincristine, doxorubicin [Adriamycin], dexamethasone) may be preferable for such patients.
- A randomized controlled trial (RCT) in abstract form that compared high-dose melphalan plus total body irradiation (TBI) versus high-dose melphalan did not find a difference in terms of response and two-year event-free survival, but toxicity was significantly greater for patients receiving the total body irradiation regimen.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Imrie K, Makarski J, Esmail R, Meyer R. Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Oct [online update]. 35 p. (Practice guideline report; no. 6-6). [106 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Dec 22 (revised 2003 Oct)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support. Summary. Toronto (ON):

Cancer Care Ontario (CCO), 2000 Dec 22 (updated online 2002 Apr). Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 29, 2002. The information was verified by the guideline developer on November 15, 2002. This NGC summary was updated by ECRI on June 29, 2004. The information was verified by the guideline developer on July 19, 2004.

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